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### Pulmonary mucinous cystic tumour of borderline malignancy

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## LETTERS TO JCP

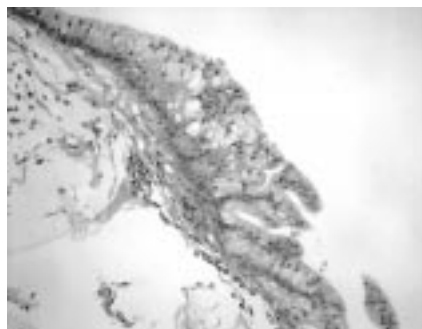
### Pulmonary mucinous cystic tumour of borderline malignancy: a rare variant of adenocarcinoma

Pulmonary mucinous cystic tumours of low or borderline malignant potential (PMTBMs) are extremely rare. These tumours have a very good prognosis and as such should be distinguished from usual type pulmonary adenocarcinoma. Here, we describe a case of PMTBM that arose in a 48 year old male non-smoker. He presented to respiratory physicians with right lower lobe pneumonia that failed to improve with antibiotic treatment. Sputum cytology revealed adenocarcinoma cells but at bronchoscopy no endobronchial tumour was seen. A right lower lobectomy was performed. Macroscopically, the lobectomy specimen contained an ill defined cystic lesion containing mucin. This measured  $15 \times 8 \times 10$  cm.

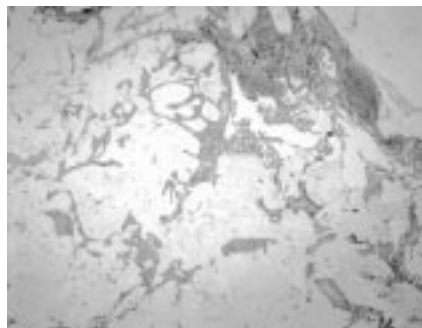
The tumour comprised tall columnar mucin secreting cells with minimal cytological atypia (fig 1) and no mitoses. The tumour cells lined spaces containing mucin and scattered single cells. No solid tumour areas were identified. Mucus dissection through the peribronchial spaces in a manner reminiscent of pseudomyxoma peritonei was seen (fig 2).

Tumour cells expressed cytokeratin 20 (CK20) strongly and CK7 weakly (fig 3). CK7 staining was also seen in pneumocytes and respiratory epithelium. There was focal expression of epithelial membrane antigen by tumour cells; however, there was no expression of carcinoembryonic antigen or chromogranin A. There was no evidence of metastatic carcinoma in the lymph nodes identified. The surrounding lung parenchyma showed bronchitis and organising pneumonia.

PMTBMs are very rare, with only 38 cases having been reported to our knowledge.<sup>1-7</sup> The presentation varies from an incidental finding in an asymptomatic patient to persistent cough, chest pain, dyspnoea, pneumothorax, and pneumonia, which fails to resolve with antibiotics.<sup>1</sup> At the time of surgery, the tumours are usually staged as T2 owing to their size. Adequate sampling of the specimen is as important as in ovarian tumours because



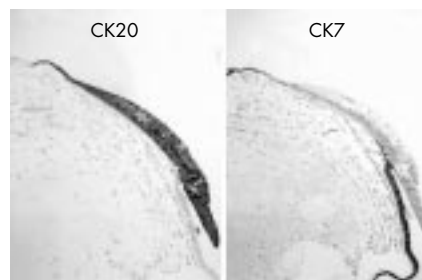
**Figure 1** Tall columnar mucin secreting cells with minimal cytological atypia (haematoxylin and eosin; original magnification,  $\times 20$ ).



**Figure 2** Mucus dissection through the peribronchial spaces in a manner reminiscent of pseudomyxoma peritonei (haematoxylin and eosin; original magnification,  $\times 4$ ).

cellularity is variable throughout these tumours. PMTBMs are histologically similar to appendiceal and ovarian mucinous tumours of borderline malignancy, with the microscopic features as described above. Lymph node involvement is not a feature.

Normal pulmonary parenchyma does not express CK20; however, pneumocytes and respiratory epithelium express CK7. Non-mucinous bronchioloalveolar carcinoma, mucinous bronchioloalveolar carcinoma, and conventional pulmonary adenocarcinomas with a bronchioloalveolar pattern at the periphery show constant but variable expression of CK7. These last two tumours also express CK20.<sup>8</sup> In our case, the tumour cells stained strongly with CK20 and weakly with CK7.



**Figure 3** Tumour cells stained with antibodies to cytokeratin 20 (CK20) and CK7 (original magnification,  $\times 10$ ).

The most difficult microscopic distinctions are between PMTBM and cystic bronchioloalveolar carcinoma and PMTBM and bronchioloalveolar carcinoma arising from a congenital cyst. Cystic bronchioloalveolar carcinoma tends to be more cellular than PMTBM, with cysts often formed secondary to necrosis,<sup>9</sup> and previously normal x rays may exclude bronchioloalveolar carcinoma arising from congenital cysts. The exclusion of metastases from the ovary, appendix, and pancreas requires comprehensive clinical and radiological examination because immunohistochemistry is unlikely to be helpful. Other differential diagnoses include non-neoplastic mucinous cysts, mucinous cystadenoma of the bronchus, and mucocoeles. These lack the cytological atypia and paucicellular mucus dissection of peribronchial spaces seen in PMTBM.

The term borderline implies a tumour of low malignant potential, rather than a tumour of no malignant potential, and this is reflected in the five year survival figures. Graeme-Cook *et al* stated that inherent in the diagnosis of borderline malignant tumour is an expected five year survival rate of between 75% and 95%.<sup>1</sup> The optimal curative treatment for these tumours is surgery. In view of the excellent prognosis of PMTBM, these tumours should be distinguished from conventional pulmonary adenocarcinomas.

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# Renal oncocytoma with a novel chromosomal rearrangement, der(13)t(13;16)(p11;p11), associated with a renal cell carcinoma

Oncocytoma is a benign epithelial tumour that makes up approximately 5–7% of primary renal neoplasms.<sup>1</sup> This tumour can be bilateral or multifocal and in 10% of cases there is an association between oncocytoma and renal cell carcinoma.<sup>2</sup> We report the case of a renal oncocytoma associated with a necrotic and cystic clear cell carcinoma. A cytogenetic study of the oncocytoma showed a new chromosomal rearrangement, namely: der(13)t(13;16)(p11;p11).

A 75 year old man with an unremarkable medical history presented with abdominal pain. Echotomography and an abdominal computed tomography scan showed two solid tumours in the right kidney. The first tumour measured 4.5 cm, was located at the lower pole of the kidney, and appeared to be necrotic. The second tumour measured 3 cm, was homogeneous, and was located in the periphery of the first tumour. A radical right nephrectomy was performed.

Gross examination showed two tumours at the lower pole of the kidney. The first tumour measured 4.5 cm in its largest diameter. It was partially cystic and largely necrotic. The second tumour measured 3 cm. It was solid, homogeneous, and had a brown to mahogany colour.

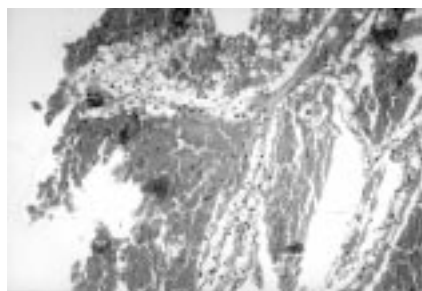
Fresh samples of the tumours were immersed in RPMI for short term culturing. Failure of the culture was observed for the large necrotic tumour.

The kidney was immersed in 10% buffered formalin and routinely processed for paraffin wax embedding; 4 µm sections were cut and stained with haematoxylin and eosin and safran. Histochemical study was performed using the Hale's colloidal iron staining (Mowry's method). Sections from paraffin wax embedded material were stained with a panel of antibodies using the streptavidin–biotin–peroxidase complex technique. The antibodies used were: pancytokeratin (KL1; Immunotech, Marseille, France; 1/150 dilution), anticytokeratin 7 (Dako, Trappes, France; 1/150 dilution), and antivimentin (Dako; 1/100 dilution).

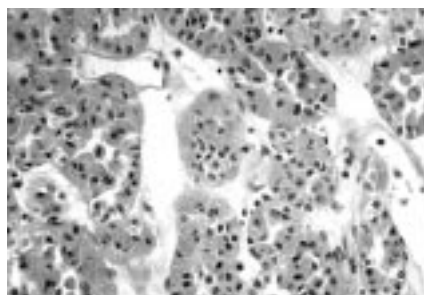
Cytogenetic analysis was performed on RHG (R bands obtained by heating and Giemsa) banding metaphases according to conventional procedures. Multitarget fluorescence in situ hybridisation (M-FISH) techniques were also performed on metaphase spreads to confirm the cytogenetic abnormality (Spectra Vysion DNA probe; Vysis, Downers Grove, USA). The M-FISH result was confirmed by specific chromosome painting (Oncor, Qbiogene, Illkinch, France). Specific telomeric probes (Cytocell, Banbury, UK) of this chromosome defined which arm was implicated in the translocation.

On microscopic examination, the first tumour was largely necrotic and a few sheets of tumour cells were identified (fig 1). The tumour cell cytoplasm was large and clear. The nuclei were round to oval, with a central nucleolus (Furhman's nuclear grade II). No granular cells were found. Immunohistochemical staining of the clear cell tumour showed positivity with antibodies to pancytokeratin and vimentin, and negativity for cytokeratin 7.

The second lesion was entirely composed of nests and tubulocystic structures of large



**Figure 1** Necrotic and haemorrhagic tumour with sheets of large clear cells.



**Figure 2** Typical oncocytoma composed of large granular cells arranged in tubulocystic structures.

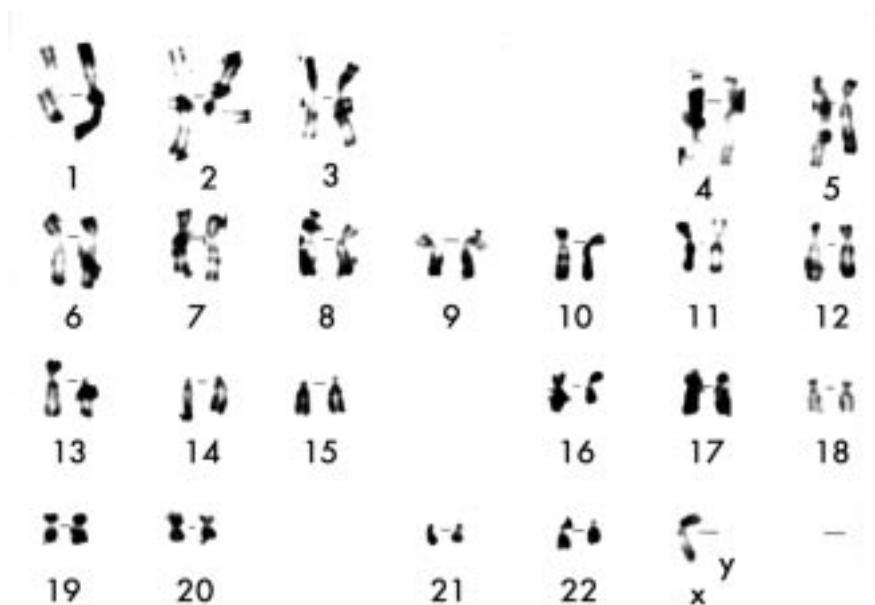
eosinophilic and granular cells (fig 2). The nuclei were round or oval with minimal atypia. A small nucleolus was frequently seen. No necrosis or areas of clear cells were observed. The mitotic count was low (one mitotic figure/20 high power fields).

Hale's colloidal iron staining was negative. Oncocytic cells were positive with antibody to pancytokeratin but staining for vimentin and cytokeratin 7 was negative.

Karyotyping of oncocytic cells showed a loss of the Y chromosome and a translocation of a piece of an autosome on chromosome 13 (fig 3). M-FISH analyses identified the addition to chromosome 13 to be a partial chromosome 16 translocation (fig 4) (confirmed by 16 specific whole chromosome painting). After FISH studies, the result of this karyotype was: 45, X,

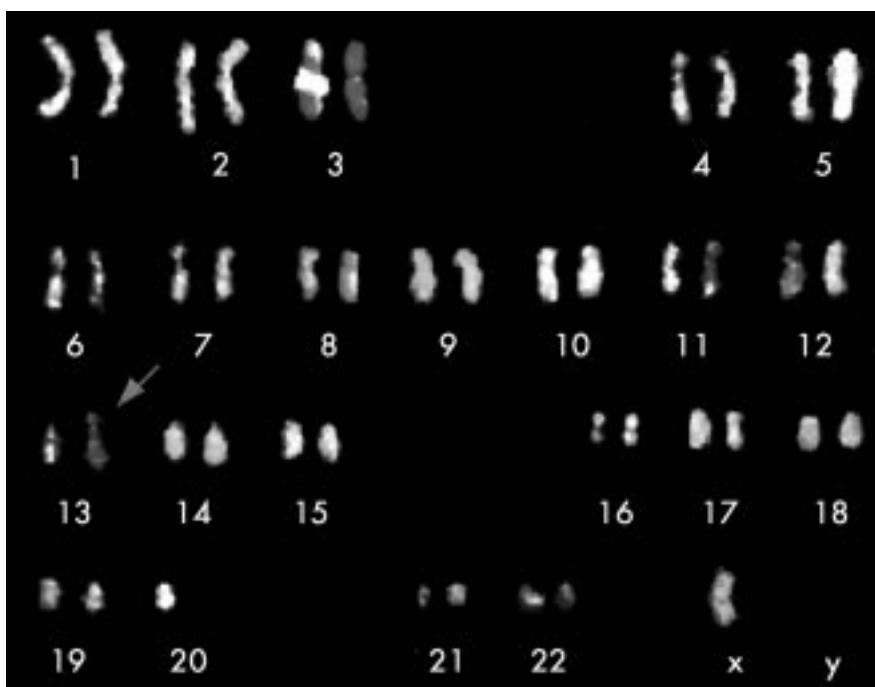
add(13)(p11.ish der(13))t(13;16)(p11;p11) (wcp16+),inv(16qh). This unbalanced 16 translocation induces a complete 16p trisomy.

Renal oncocytoma is a benign epithelial neoplasm which is now well defined.<sup>1</sup> Histological criteria are: tumour composed of an exclusive or predominant component of granular eosinophilic cells arranged in nests or tubulocystic structures. Areas of clear cells, pronounced necrosis, and papillary formations are lacking by definition.<sup>1</sup> Dechet *et al* reported bilaterality and multicentricity in 5% of cases and an association with renal cell carcinoma in 10%.<sup>2</sup> The main differential diagnosis for oncocytoma is chromophobe renal cell carcinoma. Cytological features (wrinkled nuclei, perinuclear halos, binucleation), histochemical staining (positivity of Hale's iron staining), and ultrastructural study (intracytoplasmic microvesicles) are helpful for the diagnosis of chromophobe cell carcinoma.<sup>3</sup> Cytogenetic studies showed different profiles. In chromophobe renal cell carcinoma, the most common karyotypic abnormalities are: loss of chromosomes 1, 2, 6, 10, 13, 17, and 21.<sup>4</sup> Cytogenetic studies of oncocytomas have reported several clonal abnormalities but no recurrent aberration. The most common are loss of chromosome Y or 1.<sup>5</sup> Translocations affecting chromosome 11 have also been described, namely: t(9;11)(p23;q23)<sup>6</sup> and t(5;11)(q35;13).<sup>7</sup> Other rare chromosome rearrangements have been reported, such as: t(1;12)(p36;q13),<sup>9</sup> loss of chromosome 14,<sup>10</sup> and gain of chromosome 12.<sup>5</sup> In a recent study, Tickoo *et al* reported 14 cases of diffuse renal involvement by numerous oncocytic nodules with features of oncocytoma and chromophobe renal cell carcinoma.<sup>11</sup> These authors proposed the term renal oncocytosis. They also suggested that these lesions may constitute a morphological spectrum of oncocytic tumours. Dijkhuizen *et al* proposed that renal oncocytoma characterised by loss of chromosomes 1 and Y may progress to chromophobe renal cell carcinoma with subsequent losses of chromosomes 2, 6, 10, 13, 17, and 21.<sup>12</sup> Here, we describe an additional new chromosomal rearrangement, der(13)t(13;16)(p11;p11), in a morphologically typical oncocytoma.



**Figure 3** Complete karyotype of one metaphase cell showing: 45, X, add(13)(p11).





**Figure 4** Multitarget fluorescence in situ hybridisation study showing p16 trisomy by unbalanced 16 translocation (arrow).

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## BOOK REVIEWS

### Practical Review of Neuropathology.

Gregory N, Fuller J, Goodman C. 2001, Lippincott Williams & Wilkins, \$69.95. ISBN 0 7817 2778 2

This book achieves the authors' stated objective of being a succinct overview of contemporary neuropathology. In 343 pages and 17 chapters they have produced a practical book which is a mine of accessible information. With three short chapters on cell control, neurochemistry, and neurogenetics, and two longer chapters describing the cells of the nervous system and neuroanatomy, they introduce the basic scientific concepts of the subject. The next 10 chapters focus on diseases of the central nervous system but also include a chapter on neuromuscular disorders. A section on disorders of peripheral myelin is found in the chapter on demyelinating diseases. The book ends with a chapter on the "Ten most common mistakes in surgical neuropathology" and a "Lexicon of neuropathology" where definitions, comments on the uses of stains, and examples of redundant terminology are found. Each chapter is well organised and most start by indicating the perspective of the topic and a list of objectives. As "confessed and unrepentant lumpers" the authors provide many bold diagrams and text boxes giving useful frameworks for addressing the often incompletely understood prob-



lems of pathogenesis. The numerous photographs are all monochrome, and some, lacking in detail and contrast, are not helpful. However, this is a relatively minor problem. This book does exactly what it sets out to do and, with only six references, is that refreshing rarity, the authors' view of the subject. It can be confidently recommended to all interested in neuropathology, especially trainees, and to those in general pathology.

**J E McLaughlin**

### Brain Drug Targeting: The Future of Brain Drug Development.

Pardridge W M. Cambridge University Press, 2001, £65.00. ISBN 0 521 80077 3

This very timely book describes the state of the art techniques to target drugs to the brain. For almost 30 years, the author has been an inspiring advocate for this field, and is the author of close to 300 papers in international peer reviewed journals on this subject.

Neuro(patho)logists consider the blood-brain barrier as an irreducible fortress. However, it houses active transport mechanisms for large pharmacologically engineered molecules that can also be protected from being cleared from the blood and peripheral degradation. All the essential and state of the art science and technology to target drugs to the brain has been incorporated into this book and placed in the context of the philosophy of the author. This has the advantage that it is in a single context, but at the same time it is limited to the view of only one person. Nevertheless, this approach is very important to provide a fast and fundamental insight into the various aspects of drug targeting to the brain.

This book is a comprehensive overview on the various possibilities of targeting drugs to the brain, including invasive brain drug delivery, lipid mediated and carrier mediated transport of small molecules, receptor mediated transcytosis of peptides, vector discovery for brain targeting, linker strategies for multi-drug formulations, protein neurotherapeutics and peptide radiopharmaceuticals, antisense neurotherapeutics and imaging gene expression, gene therapy of the brain, and the future: blood-brain barrier genomics.

Pardridge has provided us with a book that will become a standard on drug targeting to the brain and adds to future hope on curative instead of palliative treatment of central nervous system diseases. The book is a must for everybody who works in the field of brain drug delivery in academia as well as in the pharmaceutical industry. Finally, the book is well referenced with up to date references and includes a convenient subject index.

**W Kamphorst, A G de Boer, P J Gaillard**

## CALENDAR OF EVENTS

*Full details of events to be included should be sent to Maggie Butler, Technical Editor JCP, The Cedars, 36 Queen Street, Castle Hedingham, Essex CO9 3HA, UK; email: maggiebutler@pilotree.prestel.co.uk*

### British Association of Ophthalmic Pathology

21–22 March 2002, Dunchurch Conference Centre, Dunchurch, Rugby, UK  
*Further details:* Dr D Snead, Pathology Department, University Hospitals Coventry and Warwickshire, Coventry CV2 2DX, UK. (Tel +44 02476 538855; Fax +44 02476 538715; email david.snead@wh-tr.wmids.nhs.uk)

### Surgical Pathology for the Practising Pathologist: Selected Topics

22–25 March 2002, Sanibel Harbour Resort and Spa, Fort Myers, Florida, USA  
*Further details:* Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, MA02117-0825, USA. (Tel +1 617 384 8600; Fax +1 617 384 8686; email hms-cme@hms.harvard.edu)

### Diagnostic Histopathology of Breast Disease

22–26 April 2002, Hammersmith Hospital (Imperial College Faculty of Medicine), London, UK  
*Further details:* Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK. (Tel 020 8383 3117/3227/

3245; Fax 010 8383 2428; e-mail wcc@ic.ac.uk)

### Short Course on the Autopsy

25–28 June 2002, Department of Pathology, University of Sheffield, Sheffield, UK  
*Further details:* Mrs S Clary, Department of Pathology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK. (Tel; +44 0114 271 2501; Fax +44 0114 278 0059; email s.clary@shef.ac.uk)

### Diagnostic Histopathology

8–19 July 2002, Department of Pathology, University of Sheffield, Sheffield, UK  
*Further details:* Mrs S Clary, Department of Pathology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK. (Tel; +44 0114 271 2501; Fax +44 0114 278 0059; email s.clary@shef.ac.uk)

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